REMARKS

Status of the Claims

Claims 15, 18 and 19 are pending in the application. Claims 15, 18 and 19 are rejected.

Claims 15 and 19 are amended herein. No new matter is added to the amended claims.

Claim amendments

Claim 15 is amended to overcome the 35 U.S.C. §112, first paragraph rejection. Amended claim 15 is drawn to a method of diagnosing a Wnt antagonist-associated lytic bone disease in an individual. This method comprises examining the expression of the human homologoue of Dickkopf-1 (DKK-1) protein in the individual, where an increased expression of the protein compared to that in a normal individual indicates that the individual has the risk of developing the Wnt antagonist-associated lytic bone disease.

Claim 19 is amended to properly recite the limitation of claim 15. Amended claim 19 recites individual to have multiple myeloma.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 15 and 18-19 are rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. Applicant respectfully traverses ths rejection.

The Examiner states that there is no reasonable guidance with respect to assessing the risk of any disease and/or disorder in the instant specification. The Examiner cites **Chappuis** *et al.* and **McLaughlin** *et al.* that teach the importance of family history and environmental factors for cancer, which are the same while assessing the risk of a bone disease as taught by **Stevenson** *et al* to support the rejection. Furthermore, the Examiner states that since the specification only suggests diagnosis of bone disease in multiple myeloma patient and lacks teaching of the use of this method in determining the risk of developing any and/or all bone disease, undue experimentation would be required to practice the invention as broadly claimed.

Applicant has amended claim 15 as discussed supra. The amended claim is now drawn to diagnosing a Wnt antagonist-associated lytic bone disease in an individual. The Wnt signaling pathway is critical for osteoblast differentiation and function. Targeted disruption of low-density lipoprotein 5 (LRP5) could lead to low bone mass phenotype and gain of function mutation in LRP5 could lead to high bone mass. Furthermore, DKK1 binds to LRP5/LRP6 and disrupts the Fz-LRP5/LRP6 association (page 20, line 1-page 21, line 19). Despite this

information, it was not known whether DKK1 by itself or in combination with FRZB and LRP5 could lead to lytic bone disease. Multiple myeloma is associated with lytic bone disease and local bone destruction.

The instant invention compared the expression profile of approximately 12,000 genes in CD138-enriched plasma cells from newly diagnosed multiple myeloma patients exhibiting no lytic lesions with those having ≥3 lytic lesions to identify the genes that contributed to the lytic bone disease, (Table 1; Example 1: Example 9). The instant invention demonstrated that DKK1 and FRZB known in the art to be Wnt-signaling antagonist were not only expressed in a greater numbers of lytic bone lesions compared to the samples lacking bone lesions but that they were expressed at higher levels in plasma cells of focal lesions than in bone marrow aspirates (Example 10). Moreover, the level of expression of these genes was consistent with the expression profile when examined immunohistochemically (Example 15). More significantly, the instant invention demonstrated that these genes were not expressed in Waldenstrom's microglobulinemia, a related plasma cell malignancy that lacks bone disease (Example 11). Furthermore, the instant specification also disclosed a positive correlation between DKK1 gene expression and level of DKK1 in bone marrow plasma in patients diagnosed with myeloma using ELISA (Example 16). Thus, Applicant contends that the teachings of the instant invention demonstrate that DKK1 can be used to diagnose Wnt antagonist-associated lytic bone disease.

Applicant respectfully submits that the specification need not contain an example if the invention is otherwise disclosed in such a manner that one skilled in the art will be able to practice it without undue amount of experimentation. Because only an enabling disclosure is required, Applicant need not describe all actual embodiments" (M.P.E.P. 2164.02). In this case, the diseases such as multiple myeloma, osteoporosis, post-menopausal osteoporosis, malignancy-related (prostate cancer metastasis, breast cancer metastasis) bone loss are known in the art to be associated with bone lysis. Given the teaching in the instant specification, one skilled in the art can easily diagnose an individual suffering from any one of these diseases with Wnt antagonist-associated lytic bone disease by comparing the expression level of DKK-1 protein of such individuals with the expression of the protein of normal individuals.

Further, the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the patent coupled with the information known in the art without undue experimentation (M.P.E.P. 2164.01). As discussed supra, Applicant submits that the instant specification has provided sufficient enablement for using the claimed method to identify individuals having a risk of developing lytic bone disease. Thus, the scope of the claimed invention is commensurate with the enablement provided. Based on the above-mentioned amendments and remarks, Applicant respectfully requests the withdrawal of rejection of claims 15, 18 and 19 under 35 U.S.C. §112, first paragraph.

This is intended to be a complete response to the Final Office Action mailed January 12, 2006. Applicant submit that the pending claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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